Journal of Labelled Compounds and Radiopharmaceuticals
J. Labelled Cpd. Radiopharm. **42**, 877-883 (1999)

SYNTHESIS OF RADIOACTIVE SULINDAC-SULFONE-LACTONE VIA SULFONIUM SALT AND ^{14}C ALKYLHALIDE

Gerhard J. Sperl, PhD[+], Rifat Pamukcu, MD[#], Klaus Brendel, PhD[^], Paul H. Gross[+*]

University of the Pacific, Stockton, California, 95211: Department of Chemistry[+*]; Cell Pathways, Inc.[#], Horsham, Pennsylvania; University of Arizona, Tucson, Arizona: Department of Pharmacology[^].

SUMMARY

A new method of radioactive labeling via sulfonium salts and ^{14}C alkylhalides is reported, along with a novel synthesis of (E)-rac-(2'-buten-1',4'-olido)-[3',4':1,2]-6-fluoro-2-methyl-3-(4-[^{14}C-methyl]-sulfonylbenzylidene)-indan (scheme 1, compound $^{14}CH_3$-SO_2-L), a drug that showed very high activity, when tested in various tumor cell lines (1).

Key words: Carbon-14, Sulfonium salt, Sulindac-Sulfone-Lactone.

INTRODUCTION

In drug syntheses, many carbon atoms could be labeled in order to determine their metabolic fates. However, economy and safety dictate that the radioactive label should be introduced as late as possible in the synthesis.

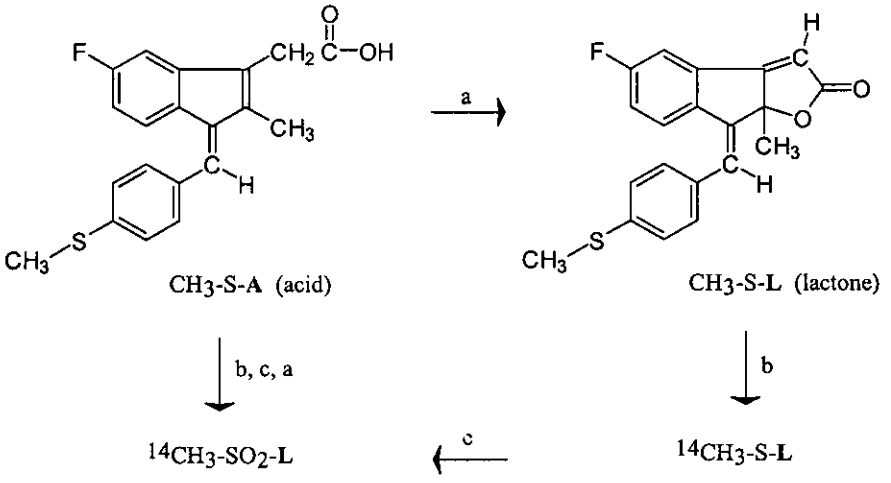
Sulfonium salts are well known in the literature (2,3), but were apparently not used for the incorporation of ^{14}C labels into R-S(O)$_n$-group containing compounds, with n = 0, 1, 2. We wish to report here a highly efficient method of radioactive labeling of sulfides via sulfonium salts and ^{14}C

CCC 0362–4803/99/090877–07$17.50

Received 27 March 1998
Revised 24 February 1999
Accepted 1 March 1999

alkylhalides, which avoids the alkylation with ^{14}C alkylhalides (4) of mercaptans, associated with stench, oxidation lability, and side reactions such as Michael additions (5). These may occur during our synthesis of (E)-rac-(2'-buten-1',4'-olido)-[3',4':1,2]-6-fluoro-2-methyl-3-(4-[^{14}C-methyl]-sulfonylbenzylidene)-indan ($^{14}CH_3$-SO_2-L). Our method avoids these problems, and could be applied in the radioactive synthesis of a new generation of selective cyclooxygenase-2 inhibitors and orally active anti-inflammatory agents, which contain methylsulfonylgroups (6,7). The inert $^{14}CH_3$-SO_2-groups would survive most catabolic steps (8).

Scheme 1.



Reaction conditions:
a) 1) NBS, 2) $^{i}Pr_2EtN$; b) $^{14}CH_3I$ / NaI; c) OXONE.

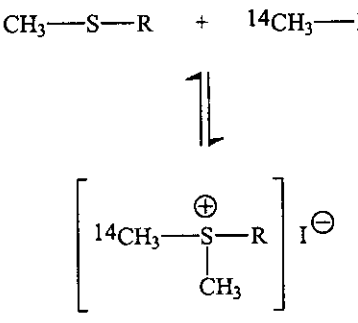
CHEMISTRY

A "traditional" 8-step synthesis of (E)-rac-(2'-buten-1',4'-olido)-[3',4':1,2]-6-fluoro-2-methyl-3-(4-[^{14}C-methyl]-sulfonylbenzylidene)-indan $^{14}CH_3$-SO_2-**L**, would require a 6-step radioactive synthesis of the precursor $^{14}CH_3$-S-**A**, from 4-[^{14}C-methyl]-thiobenzylmagnesium chloride (4,9,10,11). CH_3-S-**A** is the immediate precursor in the synthesis of Sulindac (8) CH_3-SO-**A**. The radioactive Grignard reagent is available in a 3-step sequence (4,11) from thiophenol and $^{14}CH_3I$. Oxidation of

the sulfide $^{14}CH_3$-S-**A** with OXONE (12) would give Sulindac-sulfone $^{14}CH_3SO_2$-**A**, which would lead in a halolactonization-elimination reaction (1) to the $\Delta^{\alpha,\beta}$ - butenolide $^{14}CH_3$-SO_2-**L**, (E)-rac-(2'-buten-1',4'-olido)-[3',4':1,2]-6-fluoro-2-methyl-3-(4-[^{14}C-methyl]sulfonylbenzylidene)-indan.
By contrast, our new method of radioactive labeling with [^{14}C-methyl]iodide sulfonium salts leads to the same $\Delta^{\alpha,\beta}$ - butenolide $^{14}CH_3$-SO_2-**L**, (E)-rac-(2'-buten-1',4'-olido)-[3',4':1,2]-6-fluoro-2-methyl-3-(4-[^{14}C-methyl]-sulfonylbenzylidene)-indan , in two steps.

The label is incorporated according to scheme 2, and leads to $^{14}CH_3$-S-**L**. The SN_2 equilibrium can be shifted forward by $^{14}CH_3I$ and backwards by NaI. An excess of $^{14}CH_3I$ can easily be recycled.

Scheme 2.



Sulfonium salt

The second step is the oxidation of ^{14}C-sulfide lactone $^{14}CH_3$-S-**L** with OXONE (12) in DMA/H_2O to give $^{14}CH_3$-SO_2-**L**.

RESULTS AND DISCUSSION

Our labeling method of CH_3-S-groups was first tested cold with CD_3I. The actual ^{14}C radioactive syntheses were done at Amersham with $^{14}CH_3I$. Compounds CH_3-S-**A** and CH_3-S-**L** were allowed to react with CD_3I at a certain NaI concentration. The high iodide concentration (1.2 M in the case of CH_3-S-**A**, 0.66 M for CH_3-S-**L**) pushes the equilibrium backwards and either CH_3I or CD_3I were

eliminated from the sulfonium intermediate. Variation of the CD_3I : sulfide (CH_3-S-**A** or CH_3-S-**L**) ratio gave different incorporation rates, which were determined by ^{1}H-NMR spectroscopy. If the CH_3 group of compound CH_3-S-**A** is replaced by a CD_3 group, the signal at δ 2.54 (s, CH_3-S) decreases. Integration and comparison with the signal at δ 2.15 (s, =C-CH_3) allowed the calculation of the incorporation rate. In case of lactone CH_3-S-**L** the signals at δ 2.52 (s, CH_3-S) and δ 1.69 (s, O-C-CH_3) were compared with each other. The CD_3I : CH_3-S-**A** ratio 1:1 gave about 50 %, 2:1 60 %, and 4:1 gave about 70 % incorporation. A CD_3I : CH_3-S-**L** ratio 8:1 gave about 90 % incorporation.

The actual radioactive syntheses with $^{14}CH_3I$ (55 mCi/mmol) and with a $^{14}CH_3I$: sulfide (CH_3-S-**A** or CH_3-S-**L**) ratio of 2:1, which incorporated a $^{14}CH_3I$ recycling step, led to $^{14}CH_3$-S-**A** (35 mCi/mmol; 64 % incorporation) and to $^{14}CH_3$-S-**L** (38 mCi/mmol; 69 % incorporation). Higher ^{14}C incorporation rates could be achieved by higher $^{14}CH_3I$ concentrations. However, this is usually not done, because for testing in vivo, compounds with lower specific activity are needed.

Oxidation of the radioactive sulfides $^{14}CH_3$-S-**A** and $^{14}CH_3$-S-**L** with OXONE led to the formation of the sulfones $^{14}CH_3$-SO_2-**A** (35 mCi/mmol) and $^{14}CH_3$-SO_2-**L** (38 mCi/mmol). In all cases, except in the oxidation of $^{14}CH_3$-S-**A** to give $^{14}CH_3$-SO_2-**A** (95.7 % radiochemical recovery), the radioactivity was found almost exclusively in the product (> 99 %).

These findings allayed our fear, that $^{14}CH_3$ may be incorporated into DMSO-solvent, which can be methylated at higher temperatures (13), especially under illumination. As we had hoped, trimethylsulfoxonium iodide is less readily formed, because DMSO is a weaker nucleophile than R-S-Ar. If other alkylhalides R-I were to be used instead of CH_3I, alkylation of DMSO is even less likely (14).

EXPERIMENTAL PART

^{1}H-NMR spectra were recorded at 300 MHz (Varian Gemini 300 FTNMR spectrophotometer).

(Z)-5-Fluoro-2-methyl-1-(4-[methyl-d_3]-thiobenzylidene)-3-indenylacetic acid (CD_3-S-A): Sulfide CH_3-S-**A** (1 g, 2.94 mmol) and NaI (0.7 g, 4.67 mmol) in DMSO (4 mL) were stirred with CD_3I [a)

0.2 mL; 3.2 mmol; 1.09 equ.; b) 0.4 mL; 6.4 mmol; 2.17 equ.; c) 0.8 mL; 12.8 mmol; 4.35 equ.] in the dark (5 d; 25 °C). CH_3I and CD_3I were evaporated at 3 mm Hg. The solution was added dropwise to cold aqueous 2% $NaHSO_3$. A yellow solid was filtered off, was washed with H_2O (30 mL), and was dissolved in THF (3 mL), followed by 1N NaOH (25 mL). The solution was extracted with CH_2Cl_2 (2 x 50 mL), and was added dropwise to cold aqueous 10% HCl (100 mL). The solid was filtered off, and was washed with H_2O (30 mL) and n-hexane (30 mL) to give 0.95 g of crude CH_3/CD_3-S-A. ^{1}H-NMR ($CDCl_3$): δ 2.15 (s, 3H, CH_3), 2.54 (s, SCH_3), 3.57 (s, 2H, CH_2CO), 6.74-7.37 (m, 3H, ar.), 7.30 (s, 1H, =CH), 7.35-7.52 (AB, 4H, -Ph-S). CD_3 - incorporation rate: a) 50 % ,b) 60 %, c) 70 %.

(Z)-5-Fluoro-2-methyl-1-(4-[methyl-d_3]-sulfonylbenzylidene)-3-indenylacetic acid (CD_3-SO_2-A): To a stirred mixture of CD_3-S-A (0.34 g, 1.0 mmol) and OXONE (2 $KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$, 2.46 g, 4.0 mmol) in dimethylacetamide (DMA; 3 mL) was added H_2O (1 mL) at 0°C, slowly (0.5 h), to control the exotherm. The DMA-phase of the suspension was added slowly to ice-water (40 mL). The solid part of the suspension was washed with ethanol (3x5 mL). The ethanol phase was then also added to the ice-water. A yellow solid was filtered off, and was washed with H_2O (40 mL) and n-hexane (20 mL). Recrystallization from EtOH (3.5 mL) gave at -10°C yellow CD_3-SO_2-A (0.35g, 0.93 mmol, 93%). ^{1}H-NMR ($CDCl_3$): δ 2.16 (s, 3H, CH_3), 3.30 (s, SO_2CH_3), 6.70-7.17 (m, 3H, ar.), 7.38 (s, 1H, =CH), 7.78-8.04 (AB, 4H, -Ph-SO_2).

(E)-rac-(2'-Buten-1',4'-olido)-[3',4':1,2]-6-fluoro-2-methyl-3-(4-methylthiobenzylidene)-indan (CH_3-S-L): Synthesis according to literature (1). Recrystallization from MeOH gave CH_3-S-L. ^{1}H-NMR ($CDCl_3$): δ 1.69 (s, 3H, CH_3), 2.52 (s, 3H, SCH_3), 6.00 (s, 1H, =CHCO), 6.73 (s, 1H, =CH), 6.90-7.44 (m, 7H, ar.).

(E)-rac-(2'-Buten-1',4'-olido)-[3',4':1,2]-6-fluoro-2-methyl-3-(4-[methyl-d_3]-thiobenzylidene)-indan (CD_3-S-L): Sulfide lactone CH_3-S-L (2 g, 5.91 mmol) and NaI (8 g, 53.37 mmol) in DMSO (80 mL) were stirred with CD_3I (3 mL, 48 mmol, 8.12 equ.) in the dark (6 d; 25 °C). The work-up for CD_3-S-A was followed to give 1.91 g of crude CH_3/CD_3-S-L mixture. CD_3 - incorporation rate: 90 %. ^{1}H-NMR ($CDCl_3$): δ 1.69 (s, 3H, CH_3), 2.52 (s, SCH_3), 6.00 (s, 1H, =CHCO), 6.73 (s, 1H, =CH), 6.90-7.44 (m, 7H, ar.).

(E)-rac-(2'-Buten-1',4'-olido)-[3',4':1,2]-6-fluoro-2-methyl-1-(4-[methyl-d_3]-sulfonylbenzylidene)-indan (CD_3-SO_2-L): To a stirred mixture of CD_3-S-L (0.5 g, 1.48 mmol) and OXONE (2 $KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$, 2.27 g, 3.7 mmol) in DMA (5 mL) was added H_2O (1 mL) at 0°C, slowly (0.5 h), to control the exotherm. The mixture was stirred (1 d; 25 °C; yellow → white), and was added dropwise to ice-water (100 mL). A white solid was filtered off, was washed with H_2O (20 mL), and with n-hexane (20 mL), and was recrystallized from acetone to give at -10°C white sulfone lactone CD_3-SO_2-L (0.47 g; 1.27 mmol; 86%). ^{1}H-NMR ($CDCl_3$): δ 1.69 (s, 3H, CH_3), 3.10 (s, SO_2CH_3), 6.05 (s, 1H, =CHCO), 6.77 (s, 1H, =CH), 7.02-7.37 (m, 3H, ar.), 7.55-7.94 (AB, 4H, -$PhSO_2$).

ACKNOWLEDGMENT

P.H. Gross thanks Cell Pathways, Inc. for funding this research. G.J. Sperl thanks AMERSHAM for testing the supplied procedures with radioactive material.

REFERENCES

1. Sperl G.J., Pamuku R., Brendel K., Gross P.H. - J.Med.Chem.:submitted (1998).
2. Johnson C.R., Phillips W.G. - J. Am. Chem. Soc., 91 : 682 (1969).
3. Ngola S.M., Dougherty D.A. - J. Org. Chem., 61 : 4355 (1996).
4. Gabriel J., Seebach D. - Helv. Chim. Acta, 67 :1070 (1984).
5. Rao Y.S. - Chem. Rev., 76 : 625 (1976).
6. Huang H.C., Li J.J., Garland D.J., Chamberlain T.S., Reinhard E.J., Manning R.E., Seibert K., Koboldt C.M., Gregory S.A., Anderson G.D., Veenhuizen A.W., Zhang Y., Perkins W.E., Burton E.G., Cogburn J.N., Isakson P.C., Reitz D.B. - J. Med. Chem., 39 : 253 (1996).
7. Li J.J., Norton M.B., Reinhard E.J., Anderson G.D., Gregory S.A., Ikason P.C., Koboldt C.M., Masferrer J.L., Perkins W.E., Seibert K., Zhang Y., Zweifel B.S., Reitz D.B. - J. Med. Chem.,

39 : 1846 (1996).

8. Duggan D.E., Hooke K.F., Risley E.A., Shen T.Y., Van Arman C.G. - J. Pharmacol. Exp. Ther. , 201 : 8 (1977).
9. Shuman R.F., Pines S.H., Shearin W.E., Czaja R.F., Abramson N.L., Tull R. - J. Org. Chem., 42 : 1914 (1977).
10. Pines S.H., Douglas A.W. - J. Am. Chem. Soc., 98 : 8119 (1976).
11. Pines S.H., Czaja R.F., Abramson N.L. - J. Org. Chem., 40 : 1920 (1974).
12. Trost B.M., Breslau R. - J. Org. Chem., 53 : 532 (1988).
13. Kuhn R., Trischmann H. - Liebigs Ann., 611 : 117 (1958).
14. Koenig H., Metzger H., Seelert K. - Chem. Ber., 98 : 3712 (1965).

